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Title: Diagnostic performance of Body Mass Index, Waist Circumference and the Waist-to-Height Ratio for identifying cardiometabolic risk in Scottish pre-adolescents.

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Abstract

Background: Limited studies have examined the diagnostic performance of body mass index (BMI), waist circumference (WC) or waist to height ratio (WHtR) for identifying cardiometabolic risk (increased clustered glucose, triglycerides, mean arterial pressure and inv-HDL-cholesterol) in pre-adolescent youth.

Aim: To compare the utility of BMI, WC and WHtR as predictors of cardiometabolic risk (CMR) in Scottish pre-adolescent children.

Subjects and Methods: A cross-sectional analysis of 223 Scottish children (55.2% boys, mean age 8.4 years) was undertaken. BMI, WC and WHtR were used as exposure variables within multivariate logistic regression analysis and ROC analysis to examine the utility of these anthropometrical indices in identifying those at cardiometabolic risk.

Results: Individuals with an elevated WHtR, WC and BMI were 3.51 (95% CI: 1.71-7.23; $P < 0.001$); 2.34 (95% CI: 1.35-4.06; $P = 0.002$) and 2.59 (95% CI: 1.42-4.73; $P=0.002$) times more likely to be at cardiometabolic risk. The areas under the curves [AUC] to identify children with cardiometabolic risk were significant and similar among anthropometric indices (AUC's = 0.60 - 0.65). When stratified by BMI, both WC and WHtR demonstrated a fair to good ability for identifying those at cardiometabolic risk (AUC = 0.75 - 0.81).

Conclusions: Findings suggest that the combination of BMI with either WC or WHtR may provide an added benefit in the assessment of cardiometabolic risk amongst pre-adolescents.

Key words: Weight status, youth, obesity, cardiometabolic risk

Introduction

Given the well-established evidence linking adverse weight status in childhood as being predictive of cardiometabolic complications in adulthood (Morrison et al., 2008, Juonala et al., 2011), some have described the increasing prevalence of obesity as a global pandemic (Swinburn et al., 2011). Childhood obesity is commonly defined by body mass index (BMI, kg/m^2) due to its simplicity of measurement and available normative growth charts for age and sex that provide recommendations for practitioners to define childhood overweight and obesity. When using these growth charts it is assumed that the BMI thresholds are predictive of cardiometabolic risk but little diagnostic evidence exists. Moreover, excess visceral adiposity appears to be a stronger predictor for cardiometabolic dysfunction than total adiposity in adults (Alberti et al., 2009) leading some to question whether practitioners should still be using BMI to identify children at risk of obesity-related disorders.

The measurement of waist circumference (WC) can be used as a simple and inexpensive proxy measure of abdominal obesity and cardiometabolic dysfunction (Alberti et al., 2009) but whether BMI is a better indicator than WC for cardiometabolic dysfunction in youth is unclear. Whilst some suggest that WC may be a better indicator than BMI for identifying children at risk of cardiometabolic dysfunction (Alberti et al., 2009, Savva et al., 2000), others suggest that both measures have similar predictive abilities (Lawlor et al., 2010, Falaschetti et al., 2010). It has been proposed that a waist-height ratio (WHtR) ≥ 0.5 is a valid predictor of cardiometabolic risk irrespective of age, sex or ethnicity which may be superior than BMI to identify cardiometabolic risk in youth (Kahn et al., 2005, Adegboye et al., 2010, Freedman et al., 2007). Nonetheless, the paucity of evidence which has examined the predictive utility of these three adiposity indicators as predictors of cardiometabolic risk is

sparse and inconsistent. Whereas some authors suggest that WHtR is a better predictor of cardiometabolic risk than both BMI and WC (Kahn et al., 2005, Savva et al., 2000), others report no differences in their predictive abilities (Sardinha et al., 2016, Graves et al., 2014, Kahn et al., 2014). Moreover, previous studies have tended to focus on North American cohorts resulting in a paucity of evidence relating to cohorts living in different cultural settings.

The aim of this study was to examine the predictive utility of BMI-z and WC-z (determined using age and sex specific UK national reference values (Cole et al., 1995, McCarthy et al., 2001) as well as WHtR to identify individuals at risk of clustering of cardiometabolic risk.

Methods

In this cross-sectional study, 330 participants volunteered to participate. Participants were excluded if they did not have valid data for all outcome variables resulting in 223 children (55.2% boys, mean age 8.4 years, range 5.4 to 12.3 years) being included within the analysis. The proposed methodology for this study was outlined in detail to participants and given ethical approval by the University of the West of Scotland ethical committee.

Anthropometric Indicators:

Height was measured barefoot to the nearest 0.1cm using a portable stadiometer (Seca Stadiometer, Seca Ltd, Birmingham, UK). Weight was measured barefoot with light clothing to the nearest 0.1kg on electronic scales (Seca Digital Scales, Seca Ltd, Birmingham, UK). Waist circumference was obtained using inelastic gulick tape with BMI calculated as the weight in kilograms divided by the square of height in metres. Waist circumference (cm) was measured in a standing position midway between the lower rib and the anterior superior iliac

spine following a normal expiration (Ledoux et al., 1997) with WHtR calculated by dividing WC (cm) by height (cm). In order to facilitate the analysis of results between different genders and ages, values of each variable was standardized using the following procedures. From measured height and weight, participants were classified as obese/overweight, or a healthy weight using BMI-z scores relative to the UK 1990 BMI population reference data (Cole et al., 1995). Using software provided by the Child Growth Foundation (Pan and Cole, 2010) the following definitions were applied for healthy weight (BMI z-score <1.04, below the 85th percentile) and overweight / obese (BMI z-score ≥1.04, above the 85th percentile) individuals. Waist circumference-z scores were calculated relative to the UK 1988 reference data (McCarthy et al., 2001) using software provided by the Child Growth Foundation (Pan and Cole, 2010) with a high WC defined as ≥ the 85th percentile (z-score ≥1.04). WHtR values ≥ 0.5 were considered elevated.

Blood Pressure:

Blood pressure (mmHg) was measured in an upright seated position using an automated monitor (Omron M10-IT Blood Pressure Monitor HEM-7080IT-E, Omron Healthcare UK Ltd, Milton Keynes, UK) after participants sat quietly for 10 minutes. Blood pressure was converted to standardized z-scores using software provided by the Child Growth Foundation (Pan and Cole, 2010) with values greater than the 91st percentile considered elevated as recommended (Jackson et al., 2007) .

Blood Measures:

Capillary blood samples were obtained from the finger and analysed using a point-of-care analyser. Participants were required to fast at least 12 hours prior to sampling with breakfast provided immediately after sampling. Verbal confirmation of fasting was confirmed prior to

sampling. Blood samples obtained were transferred into a cassette sample well and placed in the drawer of the analyser to provide a measure of triglycerides (TRGS), high-density-lipoprotein cholesterol (HDL-c) and glucose (GLU). The Cholestex LDX® analyser (Cholestech Corporation, Hayward, California) has demonstrated good clinical utility with core laboratory values (r = 0.77-0.91) and meets the criteria set by the lipid standardization panel (Dale et al., 2008).

Cardiometabolic Risk Factors:

In children less than 11 years of age abnormal levels of triglycerides, HDL-cholesterol and glucose were determined based on age and gender specific monitoring thresholds proposed from the IDEFICS study (Ahrens et al., 2014). For children ≥11 years of age, reference values from the National Cholesterol Education Programmes (NCEP) Pediatric Report was used to identify abnormal triglyceride concentrations as ≥1.24mmol/L and low HDL-c levels ≤1.03mmol/L (National Cholesterol Education Program, 1992) whereas impaired fasting glucose was defined as ≥5.6 mmol/L as recommended by the International Diabetes Federation (Zimmet et al., 2007). An age and sex adjusted cardiometabolic risk score (composite z-score) was calculated for each participant using the sum of the z-scores for the following variables; glucose, triglycerides, mean arterial pressure and inv-HDL-cholesterol. The cardiometabolic risk score was dichotomized at the cut-off value mean + 1SD, to identify those participants with elevated cardiometabolic risk as described previously (Sardinha et al., 2016).

Statistical Analysis:

All data was analysed using IBM SPSS Statistics 22 (IBM Chicago, IL, USA) where $P<0.05$ was deemed statistically significant. A test of normality was conducted to determine the

distribution for each variable with the independent student's t-test then used for those variables of a normal distribution and the Mann-Whitney test used for those not of a normal distribution. Independent associations between the three anthropometric indices (BMI-z, WC-z, and WHtR) and cardiometabolic risk were examined using separate multivariate logistic regression analysis models. The presence or absence of at risk levels of the three anthropometric indices (yes/no) was used as the dependant variable with the calculated odds ratios (OR) presented with their 95% confidence intervals (CI's). Receiver operating characteristic (ROC) curve analyses were performed to demonstrate the discriminatory ability of the standardized anthropometric indices for predicting cardiometabolic risk quantified by the area under the curve (AUC). At each value the sensitivity (true-positive rate) and specificity (true-negative rate) for predicting cardiometabolic risk was calculated. The most sensitive cut-off value for the detection of adverse cardiometabolic risk was obtained from the Youden index, based on the value that maximized the sum of the sensitivity and specificity, with greater accuracy reflected in a higher score. ROC AUC values of ≥0.90 were considered excellent, 0.80–0.89 good, 0.70–0.79 fair, and <0.70 poor (Metz, 1978).

Results

As shown in Table 1, the overweight/obese group demonstrated significantly higher age and sex adjusted mean levels for BMI, WC, WHtR, systolic and diastolic blood pressure, triglycerides and cardiometabolic risk as well as lower HDL-c levels. The results from the multivariate logistic regression analysis are presented in Table 2. Individuals with an increased BMI were 2.16 (95% CI 1.03, 4.53, $P = 0.039$) times more likely to have elevated triglycerides, 2.90 (95% CI 1.09, 7.71, $P = 0.027$) times more likely to have reduced HDL-c levels, 2.48 (95% CI 1.22, 5.01, $P = 0.010$) times more likely to have elevated diastolic blood pressure, 1.91 (95% CI 1.01, 3.61, $P = 0.046$) times more likely to have ≥2 individual risk

factors and 2.59 (95% CI 1.42, 4.73, P = 0.002) times more likely to have increased cardiometabolic risk.

Participants with an increased WC were 2.84 (95% CI 0.98, 8.26, P = 0.047) times more likely to have reduced HDL-c levels, 1.73 (95% CI 1.01, 2.95, P = 0.045) times more likely to have elevated systolic blood pressure, 3.06 (95% CI 1.47, 6.38, P = 0.002) times more likely to have elevated diastolic blood pressure, 1.92 (95% CI 1.10, 3.35, P = 0.021) times more likely to have ≥1 individual risk factors, 2.76 (95% CI 1.47, 5.16, P = 0.001) times more likely to have ≥2 individual risk factors and 2.34 (95% CI 1.35, 4.06, P = 0.002) times more likely to have increased cardiometabolic risk. Participants with an elevated WHtR were 3.46 (95% CI 1.56, 7.67, P = 0.001) times more likely to have elevated triglycerides, 4.44 (95% CI 1.62, 12.13, P = 0.002) times more likely to have reduced HDL-c levels, 2.33 (95% CI 1.06, 5.12, P = 0.032) times more likely to have elevated diastolic blood pressure, 1.99 (0.96, 4.12, P = 0.016) times more likely to have ≥2 individual risk factors and 3.51 (95% CI 1.71, 7.23, P = <0.001) times more likely to have increased cardiometabolic risk.

The AUC values for the prediction of cardiometabolic risk are presented in Table 3. For all outcomes, BMI-z, WC-z and WHtR performed poorly in distinguishing pre-adolescents at elevated health risk with AUC's ranging from 0.57 - 0.65. When examining the co-occurrence of risk once participants had been stratified by BMI, the performance of both WC and WHtR improved. The optimal WC-z cut-point value for identifying co-occurrence of risk ranged from 1.78 - 1.94, which corresponded to the 96th percentile, and correctly identified 68.2% of individuals with ≥ 1 and ≥ 2 individual risk factors (sensitivity) and 68.1% and 61.3% of individuals without ≥ 1 and ≥ 2 individual risk factors (specificity). The only measure for which WC-z had good discriminatory ability (AUC = 0.81) was for

cardiometabolic risk with 74.3% of individuals accurately identified as being at risk and 67.9% not at cardiometabolic risk.

The optimal WHtR cut-point value for identifying co-occurrence of risk ranged from 0.47 - 0.51. A cut-point value of 0.47 correctly identified 65.9% of individuals with ≥ 1 individual risk factors (sensitivity) and 61.2% of individuals without ≥ 1 individual risk factors (specificity) whereas the optimal WHtR cut-point value of 0.51 correctly identified 64.2% of individuals with ≥ 2 individual risk factors and 62.7% of individuals without ≥ 2 individual risk factors. Finally, the optimal WHtR cut-point value of 0.50 correctly identified 71.4% as being at risk and 70.4% not at cardiometabolic risk.

Discussion

This study examined the predictive utility of BMI-z, WC-z and WHtR using age and sex specific UK national reference values to predict the clustering of cardiometabolic risk in a non-representative sample of Scottish pre-adolescents. Findings from this cross-sectional study suggest that the UK age and sex specific national reference values used to define overweight and obesity performed well in identifying those with elevated cardiometabolic risk profiles. Our observations are unique since to the best of our knowledge, no study has compared the predictive abilities of BMI-z, WC-z and WHtR for the assessment of cardiometabolic risk using UK population specific growth standards in a pre-adolescent population comprised of children as young as 6 years of age.

In agreement with the findings of recent studies (Graves et al., 2014, Kahn et al., 2014, Sardinha et al., 2016), our results suggest that BMI-z, WC-z and WHtR have broadly similar predictive abilities for identifying adverse levels of risk factors in overweight/obese youth.

Importantly, all three indicators were able to identify those individuals who exhibited a clustering of ≥2 or more cardiometabolic risk factors. Moreover, our observations also suggest that being overweight/obese, regardless of the indicator, was associated with a more than twofold increased odds for having clustered cardiometabolic risk when compared to individuals of a normal weight. Previous studies have shown that BMI, WC and WHtR have similar abilities in identifying youth with clustering of cardiometabolic risk (Adegboye et al., 2010, Freedman et al., 2007, Khoury et al., 2013). Our findings extend these observations in a younger pre-adolescent cohort from the UK. Knowledge that the use of UK population specific reference data is able to distinguish those who present with a clustering of cardiometabolic risk factors is clinically useful and provides insight into the utility of these anthropometric thresholds.

Findings from the ROC analysis suggested that the diagnostic accuracy of each indicator to identify individuals with clustered cardiometabolic risk, measured by the AUC, was significantly higher than what would be expected by chance (AUC > 0.5). Yet despite similar abilities, it was evident that the accuracy of all three indicators was poor even if the AUC values observed in this study are comparable to those noted elsewhere (Sardinha et al., 2016, Morandi et al., 2014). Moreover, the sensitivity of the models was low suggesting, like others (Sardinha et al., 2016), that these anthropometric measures are unable to correctly classify individuals with increased cardiometabolic risk. It should be noted nonetheless that there is not one measure of efficient standards, and thresholds can be selected depending upon the desired result. In this study the most sensitive cut-off value was determined based on the value that maximized the sum of both the sensitivity and specificity as have others (Sardinha et al., 2016).

The ROC generated cut-off values for WC-z produced values ranging from the 83 – 87th percentile which is close to the 85th percentile currently recommended to identify individuals as overweight (McCarthy et al., 2001). Despite increasing trends in waist circumference values, it is encouraging that these age and sex specific UK national reference values are able to distinguish individuals who may be susceptible to cardiometabolic risk. The ROC generated cut-off values for WHtR are broadly similar to those presented in a recent study involving UK children and adolescents (Graves et al., 2014) where the statistically optimum cut-point for the clustering of cardiometabolic risk factors ranged between 0.44 – 0.48. WHtR cut-points below 0.5 have also been suggested for the clustering of cardiometabolic risk in a large cohort of European and North American youth (Sardinha et al., 2016).The optimal ROC generated cut-off value for BMI-z to identify individuals with clustering of cardiometabolic risk ranged between the 58th and 65th percentile which may suggest that the criteria used to classify overweight status may underestimate risk in individuals whose weight is classified as normal. This finding is not unique as others have demonstrated similar findings in North American cohorts (Kakinami et al., 2012) where optimal BMI percentiles for detecting cardiometabolic risk covered a wide range of values depending upon the indicator of interest.

When combining anthropometric indices to explore the combined effect of BMI-z with both WC-z and WHtR, an added benefit in the assessment of cardiometabolic risk was noted. Our observations from the UK are in accordance with the literature which recognizes the existence of metabolically benign obesity phenotypes as well as metabolically obese, normal-weight phenotypes (Ruderman et al., 1998). Since waist measures are an effective indicator of visceral adiposity and is often cited as a key mediator of cardiometabolic dysfunction given its association with cardiometabolic risk and mortality (de Koning et al., 2007, Alberti

et al., 2009), our findings suggest that measures of visceral adiposity may predict health risks beyond that identified by BMI alone. This is an important observation given the dearth of evidence which has examined the predictive utility of BMI-z, WC-z and WHtR for identifying individuals with cardiometabolic risk from the UK, particularly when geographical location may be important when understanding the prevalence of cardiometabolic risk in youth (Sardinha et al., 2016).

Despite our promising findings, limitations should be considered. Firstly, this cross-sectional design does not allow us to confer causality. Secondly, the lack of objectively measured physical activity and dietary habits, which are well-established confounders of a number of indicators measured, are acknowledged. Furthermore, since adiposity distribution and metabolic markers of cardiometabolic disease are influenced by pubertal status, future work should ensure that maturation status is controlled for in future analysis. Finally, our sample was small and drawn from one area of Scotland which limits the generalizability of our findings. Yet, to the best of our knowledge, only one previous study (Graves et al., 2014) has examined the predictive abilities of all three anthropometrical indices with cardiometabolic risk using UK recommended thresholds whilst no other study has involved Scottish pre-adolescents. Since previous studies have tended to focus on North American cohorts, our findings add to the paucity of evidence examining the predictive utility of anthropometric indices for detecting cardiometabolic risk in children living in different cultural and geographical settings.

In summary we believe that the findings of this study make an important contribution to the literature. We have demonstrated that the current definition of BMI for overweight in the UK has a similar discriminatory ability to that of WC-z and WHtR for identifying individuals at

cardiometabolic risk. Moreover, combining BMI-z with waist measures appear to further specify the cardiometabolic risk assessment of overweight/obese pre-adolescents. Further work is needed to establish the extent to which the combinations of these anthropometrical measures are able to identify future cardiometabolic risk.

Conflicts of Interest: The authors have no conflicts of interest relevant to this article to disclose.

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Table 1 – Descriptive characteristics of participants by weight status.

Variable	Normal Weight N = 162 (72.4%)	Overweight/obese N = 61 (27.6%)	*P* value
Age (years)	8.38 ± 2.35	9.07 ± 2.45	0.568
BMI (kg/m^2)	16.19 ± 1.48	21.87 ± 3.59	<0.001
BMI-z	-0.12 ± 0.72	1.93 ± 0.77	<0.001
Waist-to-height ratio	0.44 ± 0.04	0.51 ± 0.06	<0.001
Waist Circumference (cm)	58.02 ± 4.96	69.81 ± 10.26	<0.001
Waist Circumference z score	0.55 ± 0.98	2.04 ± 0.95	<0.001
Systolic BP z score	1.31 ± 1.22	1.44 ± 1.14	0.005
Systolic BP (mmHg)	109 ± 12	114 ± 13	0.015
Diastolic BP z score	0.16 ± 1.16	0.54 ± 1.33	<0.001
Diastolic BP (mmHg)	67 ± 11	69 ± 10	0.353
Glucose z score	-0.08 ± 1.02	0.10 ± 0.86	0.857
Glucose (mmol/L)	4.83 ± 0.58	4.93 ± 0.49	0.182
Triglycerides z score	-0.09 ± 0.90	0.23 ± 1.17	0.025
Triglycerides (mmol/L)	0.75 ± 0.32	0.87 ± 0.42	0.032
HDL-c z score	0.10 ± 0.99	-0.30 ± 0.99	0.007
HDL-c (mmol/L)	1.50 ± 0.37	1.35 ± 0.37	0.008
Cardiometabolic risk z score	0.26 ± 2.05	1.51 ± 2.54	<0.001

Values presented as mean ± (SD). BMI = Body mass index; HDL-c = high-density lipoprotein cholesterol; BP = Blood Pressure.

Table 2. Multivariate-adjusted OR (95% CI) for cardiometabolic risk indicators across 3 anthropometric indices

	Body Mass Index-z		Waist Circumference-z		Waist-to-Height Ratio	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Hypertriglyceridemia	2.16 (1.03, 4.53)	0.039	1.99 (0.95, 4.17)	0.064	3.46 (1.56, 7.67)	0.001
Low HDL-c	2.90 (1.09, 7.71)	0.027	2.84 (0.98, 8.26)	0.047	4.44 (1.62, 12.13)	0.002
Impaired fasting Glucose	0.86 (0.35, 2.13)	0.742	1.98 (0.87, 4.50)	0.100	0.52 (0.15, 1.83)	0.303
Elevated systolic BP	1.26 (0.70, 2.28)	0.440	1.73 (1.01, 2.95)	0.045	1.20 (0.60, 2.40)	0.607
Elevated diastolic BP	2.48 (1.22, 5.01)	0.010	3.06 (1.47, 6.38)	0.002	2.33 (1.06, 5.12)	0.032
>1 Risk Factors	1.69 (0.89, 3.21)	0.107	1.92 (1.10, 3.35)	0.021	1.82 (0.84, 3.97)	0.127
>2 Risk Factors	1.91 (1.01, 3.61)	0.046	2.76 (1.47, 5.16)	0.001	1.99 (0.96, 4.12)	0.016
Cardiometabolic risk	2.59 (1.42, 4.73)	0.002	2.34 (1.35, 4.06)	0.002	3.51 (1.71, 7.23)	<0.001

HDL-c = high-density lipoprotein cholesterol; BP = Blood Pressure.

Table 3. AUC (95% CI) for anthropometric indices and cardiometabolic risk.

		≥ 1 Risk Factors	≥ 2 Risk Factors	Cardiometabolic risk	BMI-z + ≥ 1 Risk Factors	BMI-z + ≥ 2 Risk Factors	BMI-z + Cardiometabolic risk
Body Mass Index-z	AUC	0.57	0.59	0.62			
	95% CI	0.50, 0.65	0.49, 0.6	0.54, 0.70			
	P Value	0.073	0.054	0.002			
	Sensitivity (%)	55.3	56.7	56.3			
	Specificity (%)	51.4	54.3	44.1			
	Cut-off (z-score / %)	0.21/ 58	0.38 / 65	0.67 / 75			
Waist Circumference-z	AUC	0.63	0.63	0.65	0.71	0.73	0.81
	95% CI	0.57, 0.71	0.55, 0.73	0.56, 0.73	0.58, 0.83	0.61, 0.86	0.70, 0.91
	P Value	<0.001	<0.001	<0.001	0.010	0.002	<0.001
	Sensitivity (%)	62.3	68.2	59.8	68.2	68.2	74.3
	Specificity (%)	58.1	55.7	39.7	68.1	61.3	67.9
	Cut-off (z-score / %)	0.97/ 83	1.01 / 84	1.12 / 87	1.78 / 96	1.94/ 98	1.82/ 96
Waist-to-Height Ratio	AUC	0.58	0.58	0.60	0.70	0.72	0.75
	95% CI	0.51, 0.66	0.49, 0.67	0.53, 0.68	0.56,0.83	0.84, 0.83	0.62, 0.87
	P Value	0.043	0.047	0.009	0.013	0.020	<0.001
	Sensitivity (%)	65.1	64.4	56.3	65.9	64.2	71.4
	Specificity (%)	50.4	58.4	44.1	61.2	62.7	70.2
	Cut-off	0.44	0.45	0.46	0.47	0.51	0.50

Abbreviations: BMI, body mass index; AUC, area under the curve.